Hot off the Press

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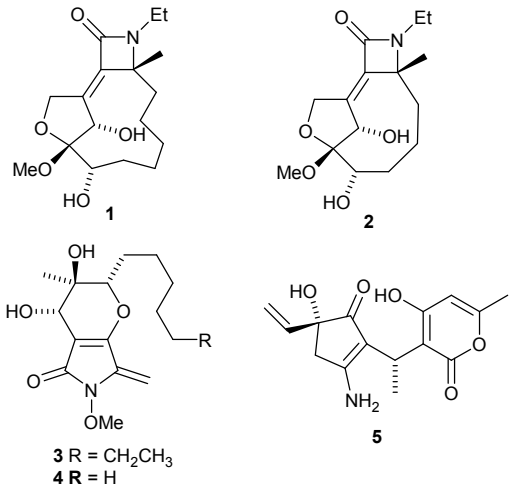
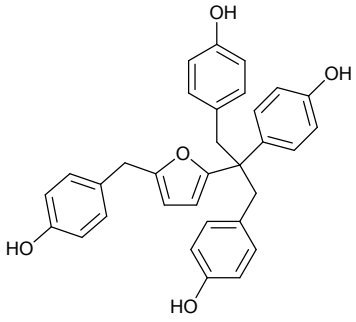
Abstract: A personal selection of 32 recent papers is presented covering various aspects of current developments in bioorganic chemistry and novel natural products such as svetamycin B from a *Streptomyces* species.

Biosynthetic labelling studies have revealed that the previously assigned structures **1** and **2** for phyllostictines A and B, fungal phytotoxins from *Phyllostica cirsii*, should be revised to **3** and **4**, respectively.[1] Phyllostictine A **3** was shown to be derived from a hexaketide and alanine. It is proposed that trichoderpyrone **5**, a metabolite of *Trichoderma gamsii*, is derived from two polyketide chains.[2]



Gastradefurphenol **6**, from *Gastrodia elata*, has a new 9,9-neolignan skeleton with the addition of two 4-hydroxybenzyl units.[3] The authors propose a biosynthetic pathway to gastradefurphenol **6**. Several hydroquinone metabolites have been isolated from a

marine-derived *Gliomastix* species including gliomastin A **7** that appears to be formed by a Diels-Alder cycloaddition of derivatives of the co-metabolites **8** and **9**.[4]



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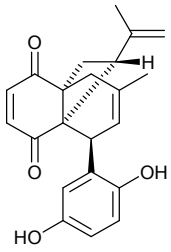

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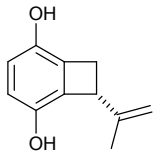

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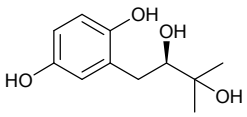

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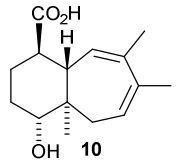
The Antarctic soil-derived fungus *Aspergillus ochraceopetaliformis* produces several sesquiterpenoid metabolites, including ochracenes A **10** and B **11**, that have new skeletons.[5] Biosynthetic pathways to ochracenes A **10** and B **11** from humulane precursors have been proposed. Xylopiana A **12** is a dimeric guaiane sesquiterpenoid from leaves of *Xylopia vielana*.[6] It is postulated that the caged structure of xylopiana A **12** is formed by a Diels-Alder cycloaddition of guaiane precursors followed by a [2+2]cycloaddition. Irradiation of the co-constituent vielanin F **13** produced xylopiana A **12** which suggests that it may be formed in nature by the action of sunlight.



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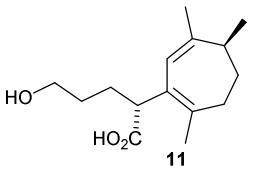

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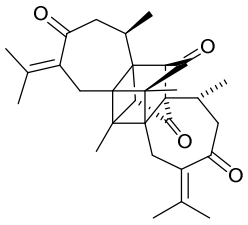

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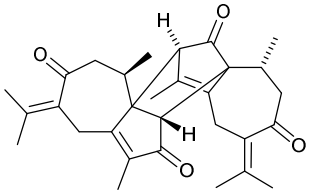

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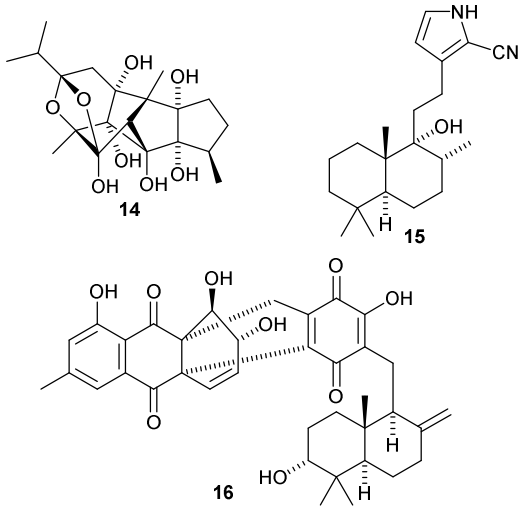
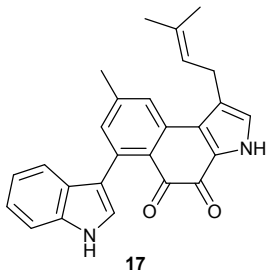
Cinnamomol A **14**, a diterpenoid from leaves of *Cinnamomum cassia*, has a novel hexacyclic ring system.[7] Vitepyrroloid A **15**, from leaves of *Vitex trifolia,* is a labdane diterpenoid with an unusual cyano-substituted pyrrole ring.[8] The structures of both cinnamomol A **14** and vitepyrroloid A **15** were confirmed by X-ray analysis and biosynthetic routes for their formation have been proposed. Neomacrophorin X **16**, a metabolite of *Trichoderma* sp. 1212-03, is the first example of a natural [4.4.3]propellane with a carbon framework.[9] The authors suggest a biosynthetic pathway involving the coupling of a dihydroanthoquinone derivative to a meroterpenoid.



The structure of cimicifoetone A **17**, a black pigment isolated from *Cimicifuga foetida*, was established by X-ray analysis.[10] Cimicifoetone A **17** is the first example of a dimeric indole alkaloid formed by the Diels-Alder addition of a prenyl side chain of one unit with the aromatic ring of another. Melosline A **18**, from *Alstonia scholaris*, has a novel ring system.[11] A biosynthetic pathway to melosline A **18** from a stemmadenine derivative has been proposed. Cyclohelminthol X **19**, a metabolite of *Helminthosporium velutinum*, contains an unusual fully substituted spirocyclopropane that appears to be formed by addition of an oxidized form of the co-metabolite cyclohelminthol IV **20** to a maleimide derivative.[12]



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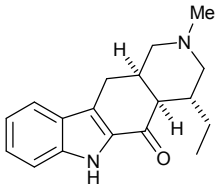

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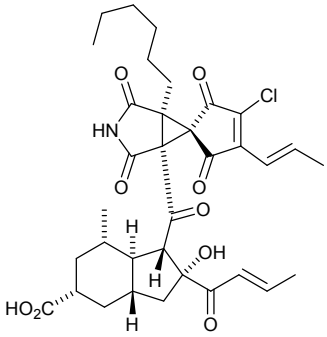

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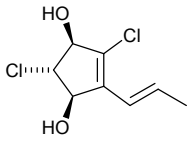

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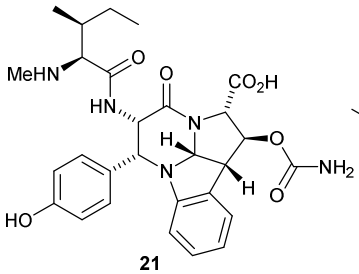
Biosynthetic studies have established that crocagin A **21**, a metabolite of *Chondromyces crocatus*, is formed from three *C*-terminal amino acids of a precursor peptide.[13] Aspochalazine A **22**, a metabolite of *Aspegillus* sp. Z4, is the first example of an azabicyclic aspochalasin.[14] The structure of aspochalazine A **22** was established by X-ray analysis and a biosynthetic pathway for its formation has been proposed involving the introduction of the bridging nitrogen from alanine by a ω-transaminase.



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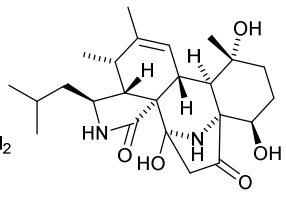

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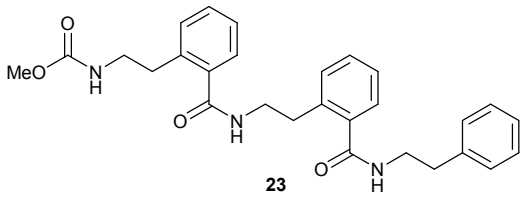
Several metabolites have been isolated from the ascidian *Didemnum molle* with repeating *o*-carboxyphenethylamide units such as mollecarbamate B **23**.[15] A biosynthetic pathway to *o*-carboxyphenethylamine from shikimic acid has been proposed. Seven halogenated peptides, such as svetamycin B **24**, have been isolated from a *Strepotomyces* species that include unusual amino acids such as δ-methylated

piperazic acid.[16] Biosynthetic studies have demonstrated that ornithine is the precursor of piperazic acid and the methylation at the δ-position is SAM-dependent.



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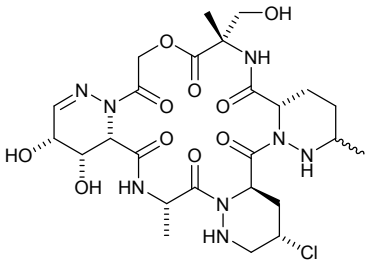

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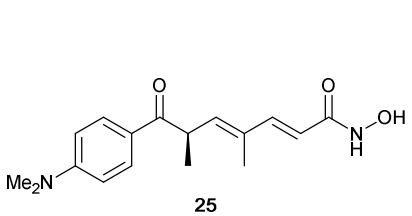
The entire biosynthetic gene cluster of trichostatin A **25**, an inhibitor of histone deacetylase from *Streptomyces* sp. RM72 has been reported.[17] This work has revealed the enzymes responsible for formation of the terminal hydroxamic acid, which involves transfer of hydroxylamine from the nonproteinogenic amino acid, L-glutamic acid γ-monohydroxamate. In a study designed to investigate the biosynthesis of the naphthalenic neoansamycins, a disrupted nam*7*-mutant strain has produced ten novel benzenic ansamycins, such as 5,10-*seco*-neoansamycin A **26**.[18] The authors propose that these are the benzenic counterparts of neoansamycins and that a putative hydroxylase, Nam7 interconverts these two classes of compounds by naphthalenic ring formation.



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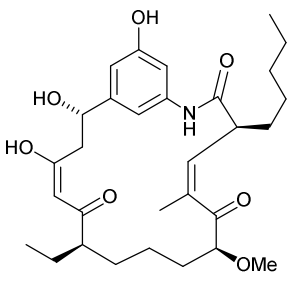

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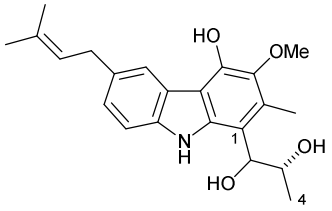
The three enzymes involved in the biosynthesis of the C4-alkyl side-chain of neocarazostatin A **27**, a bacterial alkaloid and potent free radical scavenger have been confirmed.[19] These include two pathway specific enzymes, NzsE, a free-standing acyl carrier protein and NzsF, a homolog of a β-ketoacyl-acyl carrier protein synthase III, which catalyses a Claisen condensation. Investigation of the stereospecificity of four *S*-adenosyl methionine-dependent *C*-methyltransferases from *trans*-AT polyketides synthases (PKS), including BonMT2 involved in bongkrekic acid **28** biosynthesis, all showed exclusive production of the (2*R*)-2-methyl-3-ketoacyl-ACP product.[20]



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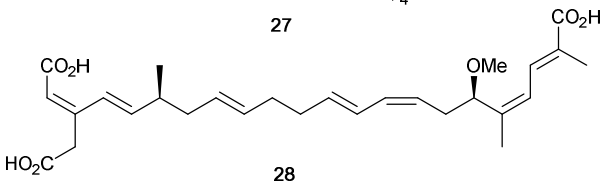

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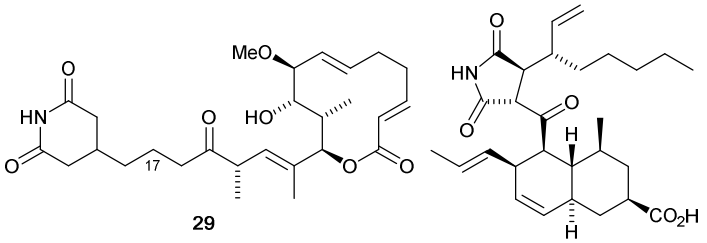
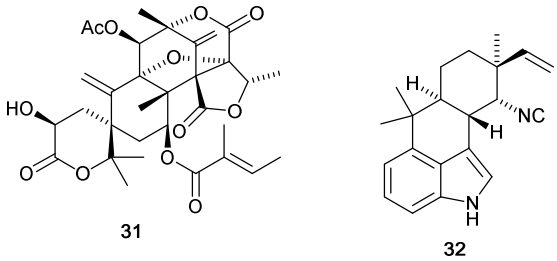
The dehydratase domain responsible for the dehydration of the C17 hydroxy group during the biosynthesis of iso-migrastatin **29**, a 12-membered macrolide from the glutarimide-containing polyketide family has been revealed.[21] Systematic inactivation of four of the dehydratase domains of the iso-migrastatin PKS and characterisation of the wild-type and mutant enzymes in vivo, identified DH10 as the enzyme which catalyses the long range dehydration of the C17 hydroxy group. A new set of natural products, such as oxaleimide A **30**, formed through the interaction of a highly reducing PKS (HRPKS) with a PKS-nonribosomal peptide synthetase (PKS-NRPS), have been isolated from *Penicillium* species.[22] The HRPKS produces an alkene containing amino acid that is incorporated by the adenylation domain of the PKS-

NRPS and forms the *trans*-decalin ring system via an intramolecular Diels-Alder reaction with a diene-containing octaketide component.

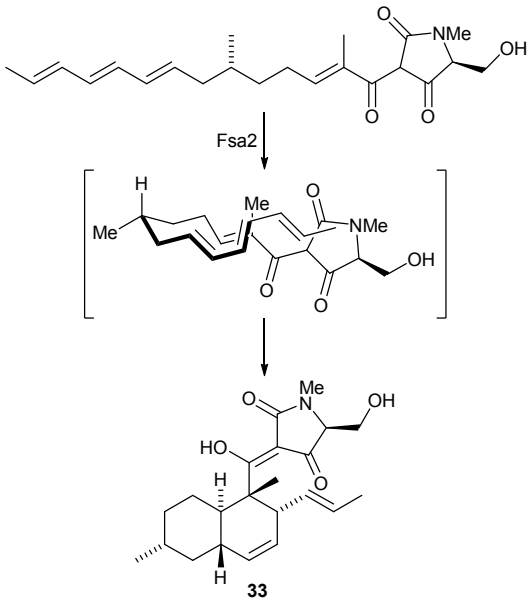


Genome mining has led to the discovery of six new putative biosynthetic genes of the austinol/dehydroaustinol biosynthetic pathway in the filamentous fungus *Aspergillus calidoustus*.[23] This allowed the characterisation of an unusual noniterative diketide synthase, which was used for the production of a new insecticidal derivative, calidodehydroaustin **31**. A new class of stigonematales cyclases that catalyse the tri- and tetracyclic core formation of indole alkaloids such as 12-*epi*-hapalindole U **32** have been reported.[24] In vitro reconstitution of the functional activities of this new class of indole alkaloid cyclases show they catalyse intramolecular ring formation through a cascade process, forming four new stereogenic centres.



The total synthesis of the fungal tetramate natural product, equisetin **33** has been reported using the Diels-Alderase Fsa2 to construct the *trans*-decalin ring system.[25] Unlike thermal or acid-mediated [4+2]cyclisation of the triene precursor, which produced a mixture of *endo* and *exo* products, the Fsa2 promoted Diels-Alder reaction proceeded exclusively via the *endo*-transition state to give equisetin **33** as the sole product (Scheme 1). The substrate scope for intramolecular benzoin reactions with

benzaldehyde lyase (BAL) from *Pseudomonas fluorescens biovar 1* has been established.[26] A range of substituted benzaldehydes connected by a five atom diether linkage proved the most effective substrates, giving the novel cyclic benzoin adducts in high yields and enantioselectivities (Scheme 2).



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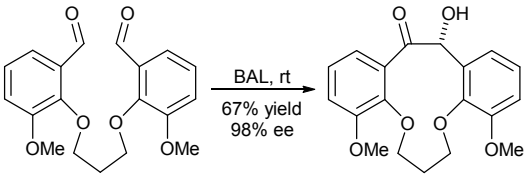
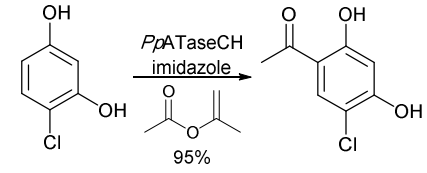
Scheme 1

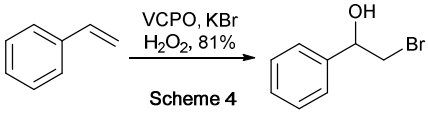


Scheme 2

A bacterial acyltransferase has been shown to perform both Friedel-Crafts acylations and Fries rearrangement-like reactions with resorcinol derivatives.[27] Using readily available *O*-acyl donors, such as isopropenyl acetate allowed highly regioselective and efficient *C*-acylation reactions (Scheme 3). The hydroxyhalogenation of alkenes for the regioselective preparation of halohydrins has been achieved using a vanadium-dependent chloroperoxidase (VCPO) from *Curvularia inaequalis*.[28] The robust nature of the enzyme against hydrogen peroxide enabled the efficient synthesis of a range of halohydrins on preparative scale (Scheme 4).

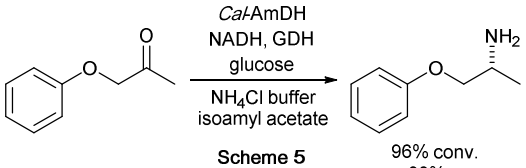


Scheme 3



Scheme 4

In an effort to overcome the limitations of amine dehydrogenases for preparative reductive amination, a study has been conducted to investigate the effect of reaction engineering, immobilised enzyme and stable engineered variants in solving these issues.[29] Using a biphasic system and an engineered amine dehydrogenase from *Caldalkalibacillus thermarum* as a lyophilised whole-cell preparation, allowed the efficient reductive amination of up to 400 mM of phenoxy-2-propanone (Scheme 5). A new (*S*)-specific carbonyl reductase (*S*RED) from the yeast *Candida parapsilosis* ATCC 7330 has been purified and used for the reduction of various aryl carbonyl compounds.[30] While minimal activity was observed with aldehydes as substrates, ketones were reduced with excellent enantioselectivity (Scheme 6).



Scheme 5

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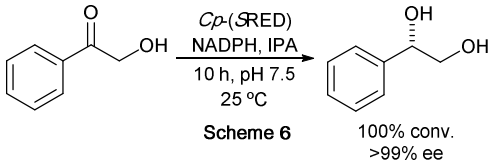

Scheme 6

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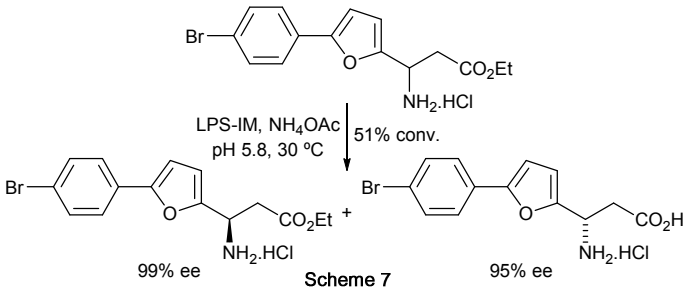
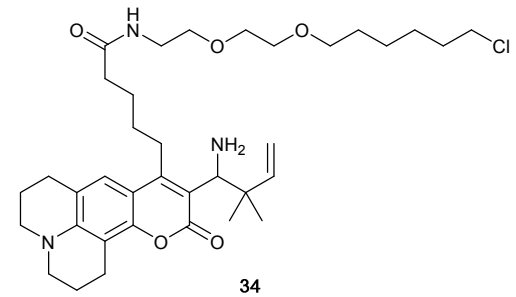
5-Phenylfuran-2-yl-β-alanine ethyl esters have been efficiently resolved using immobilised lipases such as lipase PS (LPS-IM) from *Burkholderia cepacia*.[31] Instability and solubility issues of the 5-phenylfuran-2-yl-β-alanine ethyl esters were overcome using stable hydrochloride salts that were excellent substrates for kinetic

resolution (Scheme 7). A series of ratiometric formaldehyde probe indicators have been developed for the excitation-ratiometric fluorescence imaging of formaldehyde production in living systems.[32] On reaction with formaldehyde, the coumarin derived homoallylamines (e.g. **34**) are converted to an aldehyde congener through an aza-Cope rearrangement, resulting in an approximate 50 nm shift in excitation wavelength. These probes demonstrated high selectivity for formaldehyde over other reactive carbonyl species and were used to monitor formaldehyde changes in biological samples using live-cell imaging.



Scheme 7



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